Topic 31 – Gene expression, MicroRNA, proteome

April 03rd, Friday 2015

0163

ADRB2 Gln27Glu polymorphism is associated with early ventricular arrhythmias in primary myocardial infarct

Elodie Morel (1), Gina Morgan (2), Barry London (2), Philippe Chevalier (3)
(1) CHU Lyon, Hôpital Cardiologique Louis Pradel, Rythmologie, Bron, France – (2) University of Iowa, Iowa, Etats-Unis – (3) CHU Lyon, Hôpital Cardiologique Louis Pradel, EA4612 Neurocardiologie, Lyon, France

The genetic variant rs1042714 (Gln27Glu) in ADBR2 gene coding for the β2 adrenergic receptor has been associated with sudden cardiac death and with ventricular arrhythmias in heart failure in previous population-based studies. We investigated whether the same polymorphism is associated with ventricular fibrillation (VF) in the context of myocardial Infarction (MI).

Patients have been recruited between 2008 and 2013 during the MAP-IDM study. Subjects included 213 patients who experienced a VF during acute phase of primary myocardial infarct and 181 controls with MI but without VF. None of the patients had other cardiac history. Patients were genotyped for the *ADRB2* Gln27Glu polymorphisms by RT-PCR.

Cases and controls didn't differ significantly in age (56.2±11.8 vs 57.4±11.4 years), in sex ratio (male 83.6% vs 83.4%), in smoker ratio (56.4% vs 58.0%) and in troponin peak value (64.2 +/-116.0 vs 70.0±78,7µg/L). Cases have a lower body mass index (BMI) (25.6±3.9 vs 26.7±4.1, p=0.01) and a lower left ventricular ejection fraction (LVEF) (45.8±11.9 vs 51.9±10.5%, p<0.0001).

In the total cohort, the Gln27Glu is in Hardy Weinberg Equilibrium (157Gln27Gln, 181 Gln27Glu, 56 Glu27Glu). Genotypes were not associated with age, gender, BMI, troponin, EF or smoking in univariate analyses.

The most interesting finding is that the delay of onset on VF in Gln27Glu cases is two times faster (73.1±105.6min) than cases carrying the Gln27Gln genotype (161.5±255.5min; p=0.004) or the Glu27Glu genotype (163.1± 314.9min; p=0.03). The Gln27Glu cases are more likely to have a VF in the 60 min after thoracic pain (OR=2.6, p=0.003).

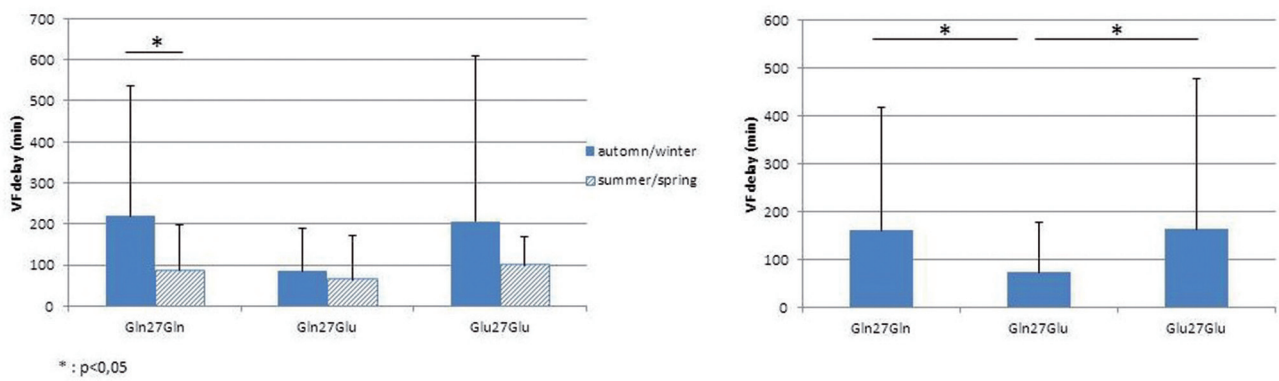
We also show that the delay of VF is twice as fast in summer/spring period than in autumn/winter period for Gln27Gln genotype (219.2vs86.7min; p=0.02) and for Glu27Glu genotype (205.4 vs 99.6min, no significative but few samples). However, we observed that this VF delay is almost the same for Gln27Glu genotype whatever the season (84.0vs64.8min)..

0399

IRESs as translational enhancers of gene expression in hypoxic cardiomyocytes

Fransky Hantelys (1), Edith Renaud-Gabardos (1), Isabelle Ader (2), Barbara Garmy-Susini (3), Angelo Parini (3), Anne Catherine Prats (1)
(1) Université Paul Sabatier, TRADGENE EA 4554, Toulouse, France – (2) CHU Toulouse Rangueil, UMR 5273 UPS-CNRS-EFS-INSERM U1031, STROMALAB, Toulouse, France – (3) CHU Toulouse Rangueil, INSERM U1048, I2MC, Toulouse, France

Ischemic heart failure is a pathology characterized by coronary arteries occlusion resulting in lack of oxygen and energy in heart muscle. In hypoxic tissues, mRNA translation is altered: global translation is blocked whereas a small number of messengers are still translated by an alternative mechanism involving RNA structure elements called internal ribosome entry sites (IRESs). Our laboratory has identified IRESs in mRNAs of several angiogenic or lymphangiogenic growth factors. In the present study, we have addressed the regulation of IRES-dependent translation by hypoxia in vitro in mouse cardiomyocytes HL-1. Bicistronic lentivectors expressing the two renilla and firefly luciferases separated by different IRESs were constructed and produced. Cardiomyocytes were transduced and submitted to hypoxic conditions. We have identified three groups of IRESs, activated in cardiomyocytes at 4h, 8h and 24h of hypoxia. To study translational regulation of gene expression in hypoxic cardiomyocytes, we purified polysomes containing translated RNAs from hypoxic cardiomyocytes and analysed gene expression using the Fluidigm deltagenes qPCR gene expression assay. Our data show that many angiogenic growth factors, except for VEGFA, are induced at translational but not at the transcriptional level. Especially, IRES containing mRNAs are associated to the polysomes of hypoxic cells, suggesting that the IRES-dependent mechanism is a crucial mechanism of response to stress in hypoxic heart tissue. The trans-acting factors responsible for IRES activation during hypoxia are under investigation. In addition, IRESs are also promising biotechnological tools to design gene transfer vectors able to co-express several therapeutic molecules. IRESs activated in ischemic conditions will be used in gene transfer IRES-based vectors to optimize expression of therapeutic genes in the gene therapy approach of heart ischemia developed in the laboratory.



Abstract 0163-Figure: Gln27Glu polymorphisms and VF delay